Faculty of Medicine
and
Prince Salman Heart Center
King Fahad Medical city
and
King Saud Bin Abdul Aziz University for Health Sciences

International Conference

4th – 5th October 2011

Venue: King Fahad Medical City
The Main Auditorium

Myocardial Protection
From Bench to Clinical Application

Recent Advances in Myocardial protection,
Including heart failure, Ischemic heart
disease and Sleep disorders.
Welcome Message from the Associate Dean of the Faculty of Medicine
Dear Colleagues,

On behalf of the Prince Salman Heart Center and the Faculty of Medicine, it is my distinct pleasure to welcome you at our Myocardial Protection (Conference) from Bench to clinical application on the 4th-5th of October 2011.

The organizing and scientific committees have worked hard to assemble an exceptional scientific program that meets the current demand of both the basic and clinical aspects of myocardial protection.

This conference will provide a great opportunity to update practitioners and medical students with the latest information in protecting and repairing cardiac muscle from damage. Our target audience includes members of Faculty, Adult Cardiology and Cardiac Surgery services, including Consultants, Assistant Consultants, Cardiology Fellows, Residents, Interns and medical students.

The aim of the symposium is to provide our cardiovascular professionals with the latest advances in the field of myocardial injury patterns and the different updated measures of protection.

Many innovative methodologies have recently emerged anywhere from nano-technology to complex Stem Cell and genetic manipulations targeting the limited number of Myocardial cells that we are born with and aiming at the restoration of lost functional units of the myocardium.

This conference has successfully attracted 10 distinguished International speakers and 10 national leaders in their fields who have graciously agreed to participate in this very ambitious program. We look forward for your participation in this upcoming event.

Mostafa A. Youssef, MD, FRCPC, FACP, FACC, FESC, FSCAI
Director of Prince Salman Heart Center
King Fahad Medical City
Dear Guests, Colleagues and Students

It is my great pleasure to welcome you all to the myocardial protection conference.

It also gives me great pleasure to welcome our international visitors to the Kingdom of Saudi Arabia “The land of generosity” and The Holy Land, which embraces the Kaaba the holiest Islamic shrine to which billions of Muslim people face in their daily prayers. The land where not just prophets, found shelter, peace and safe haven but many other people still do until today. We shall do all we can to make your stay a pleasant and comfortable one the memories will last for many years to come.

Sincere thanks to Dr Abdullah Alamro, CEO King Fahad Medical City, Dr. Abdulaziz Al Kaaba, Associate Dean of Faculty of Medicine and Dr. Mostafa Youssef, Director of Prince Salman Heart Center, who were of great help and support in the organization of the conference.

For this two days meeting we have attracted some of the best and most well known researchers from Canada, USA and UK who will share with us the latest findings (clinical and basic) on many issues related to the protection of myocardium.

This conference will provide a good opportunity for interaction between local and international scientist and clinicians and help to establish good contacts and fruitful collaboration between the different institutes. It will also give the researchers and scientists a chance to exchange ideas and share their views and experiences.

Last but by no means the least, we, at the organizing and scientific committees are grateful to our sponsors. Without their support this meeting could not have been possible.

Our sincere thanks to the CPE department in King Fahad Medical City which was our partner in the organization and arrangement of this conference.
Wishing the meeting all the success and hoping to meet you next year in a more informative and comprehensive meeting to cover more aspects of heart research.

Sincerely Yours
Said Khatib
Faculty of Medicine
King Fahad Medical City
Organizing & Scientific Committee

Chairman of the symposium:
Dr. Mostafa Youssef.
Director of Prince Salman Heart Center (PSHC)

Prof. Said Khatib – FOM – Chairman
Prof. Ali Mustafa – FOM
Dr. Samih Lawand - PSHC
Dr Abdul Aziz AlGhamdi – PSHC
Dr. Mohammed Rizwan Khalid- PSHC
Dr. Mohammed Suliman - FOM
Dr. Mohammed Adnan - FOM
Dr. Eeman At-Taras - FOM
Dr. Rajaa Mirghani – FOM
Ms. Mudawi Alotaibi-CPE
Scientific Program
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<td>Welcome note</td>
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<td>Dr. Mostafa Youssef, President of the conference</td>
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<td>Myocardial Angiogenesis: Are we there yet?</td>
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<td>Roger Laham, USA</td>
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<td>Dr. Said Khatib, Organizing Committee Chairman</td>
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<td>09:40 - 9:50</td>
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<td>Director of Academic &amp; Training Affairs, King Fahad Medical City</td>
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<td>Dr. Abdulla Alamro, CEO, King Fahad Medical City</td>
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<td>Recognition of international speakers</td>
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**Session 1**

Heart Failure, Mechanisms and Management
Chairman: Prof. Mansour Al Nuzha
Co-Chairman: Prof. Ali Mustafa

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<td>Drug Induced Heart Failure: Pathogenesis and Prevention. Pawan Singal, Canada</td>
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<td>Protect the Myocardium: New drugs to treat heart failure Diego Delgado, Canada</td>
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<td>11:10 - 11:30</td>
<td>Optimizing energy metabolism as an approach to treat myocardial ischemia and heart failure Gary Lopaschuk, Canada</td>
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<td>Interplay of cytokines in heart failure Pawan Singal, Canada</td>
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<td>01:00 - 01:20</td>
<td>The role of QRS in cardiac resynchronization therapy</td>
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<td>01:20 - 01:40</td>
<td>Echocardiography optimization of CRT</td>
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<td>01:40 - 02:00</td>
<td>The role of nuclear imaging in CRT</td>
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<td>Electrophysiological substances of sudden cardiac death</td>
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**Prayer time and Coffee Break**

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<td>Sleep disordered breathing and cardiovascular risks</td>
<td>Saleh Dammas, KSA</td>
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<td>03:40 - 04:00</td>
<td>Reperfusion injury as a target for cardioprotection</td>
<td>Derek Hausenloy, UK</td>
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<td>04:00 - 04:20</td>
<td>Autophagy in human heart</td>
<td>Salik Jahania, USA</td>
<td>USA</td>
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<td>04:20 - 04:30</td>
<td>Implication for exercise in heart failure protection:</td>
<td>Michael Welsch, USA</td>
<td>USA</td>
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<td>04:30 - 04:50</td>
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<td>Workshop I: Echocardiography in IHD</td>
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**Moderators:** Abdulaziz Alghamdi & Ziad Al Harfi
## Day 2  
**Wednesday Oct. 5th 2011**

### Session 4  
**Support of Ischemic Myocardium**  
Chairman: Dr Khalid AlHabib  
Co-Chairperson: Dr. Samih Lawand

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<td>Revascularization in ischemic cardio-myopathy</td>
<td>Samih Lawand, KSA</td>
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<td>Role of mechanical assist devices in myocardial protection</td>
<td>Salik Jahania, USA</td>
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<td>How to achieve myocardial recovery with mechanical assist devices</td>
<td>Diego Delgado, USA</td>
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<td>09:30 – 09:50</td>
<td>Role of impella in cardiogenic shock</td>
<td>Hassan Mhish, KSA</td>
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### Session 5  
**Myocardial Protection II**  
Chairman: Dr. Michael Welsch  
Co-Chairperson: Dr. Asif Hamid

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<td>Phosphodiesterase inhibitors and myocardial protection</td>
<td>Said Khatib, KSA</td>
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<td>Remote ischemic conditioning as a clinical application</td>
<td>Derek Hausenloy, UK</td>
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<td>11:10 – 11:30</td>
<td>Myocardial regeneration: Finally something that works</td>
<td>Roger Laham, USA</td>
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### Session 5
**Myocardial Protection II**
Chairman Dr. Michael Welsch  
Co-Chairperson: Dr. Asif Hamid

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### Session 6
**Metabolic Syndromes: Diabetes and Fatty acids**  
Role in cardiovascular Disease  
Chairman: Dr. Gary Lopaschuk  
Co-Chairperson: Dr. Mohammed Adnan

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<td>Progressive effects of diabetes mellitus on the heart</td>
<td>Chris Howarth, UAE</td>
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<td>Contribution of fatty acid oxidation to cardiac dysfunction in obesity and diabetes</td>
<td>Gary Lopaschuk, Canada</td>
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<td>Vascular health and performance; linking biochemistry and physiology with physical functions</td>
<td>Michael Welsch, USA</td>
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<td>Cell signaling and metabolism in diabetic heart</td>
<td>Chris Howarth, UAE</td>
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<td>02:50 – 03:00</td>
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Saleh Al-Dammas
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King Fahad Medical City

Karamony Das, MD
Consultant Chest Radiologist/ Cardiac CT, Medical Imaging Administration, King Fahad Medical City

Ziad Al Harfi, MD
Abstracts
Myocardial angiogenesis: are we there yet
Roger Laham, USA

Ischemic heart disease remains the leading cause of death. Despite advances in medical, catheter based and surgical revascularization, the progressive nature of this disease, the significant late failures of venous bypass grafts stents have resulted in an increasing number of patients that have exhausted all available treatment options yet remain symptomatic on maximal medical therapy. Therapeutic angiogenesis may help restore blood flow to ischemic myocardium. A significant body of in-vitro and preclinical data suggests that angiogenesis is feasible and indeed occur clinically. However, clinical trials to date utilizing protein, gene, or cell therapy have been disappointing with early positive results followed by larger randomized, controlled, double-blind study that showed no significant benefit. This brought to light several issues: first angiogenesis may be too complex a process to be stimulated effectively with a single angiogenic cytokine; second angiogenesis therapies may result in small benefits that may not be detectable using currently available outcome measures necessitating the development of novel endpoints; third, delivery strategies have to be optimized and tailored for the agent and cell delivered; fourth and most importantly, the placebo effect is very powerful in end stage ischemic heart disease and carries a physiologic component in terms of improved perfusion and function. The perceived complexity of the angiogenic process prompted the evaluation of master switch molecules such as the Hypoxia Inducible Factor (HIF)-1α transcription factor and the investigation of cellular therapies using skeletal myoblasts, bone marrow, and bone marrow derived, circulating, or embryonic stem cells in addition to better understanding of angiogenesis inhibitors. We will discuss all these issues with a comprehensive review of the topic, clinical data to date and future directions, with an emphasis on recent data from our angiogenesis center that sheds light on the field and establish potential collaborative strategies to achieve clinically significant angiogenesis, a need for our patients.

Drug-induced heart Failure: pathogenesis and prevention
Pawan K. Singal, Canada

Doxorubicin (Dox) is frequently used as a frontline chemotherapeutic agent against a variety of cancers. Although tremendous progress has been made on its optimal usage over the last 40 years, cardiotoxicity still remains a major concern. The great promise is that the mechanisms leading to antitumor activity appear to be different from those leading to Dox-induced cardiomyopathy. In this regard, we have provided evidence that cardiomyopathy is mediated by an increase in oxidative stress. Such an increase is a consequence of the drug-induced increase in the production of oxygen radicals and a simultaneous decrease in antioxidants, most notably in glutathione peroxidase. Our studies have drawn attention to probucol (Prob), a lipid-lowering agent with potent antioxidant properties, which provides complete protection against Dox-induced cardiomyopathy. We also documented that an adjunct therapy with Dox and Prob does not interfere with the antitumor properties of Dox in an experimental setting. Clinical trials employing Dox therapy in combination with probucol are needed to determine whether the findings in animal experiments can be extrapolated to clinical applications. (Supported by the Heart and Stroke Foundation of Manitoba.)
Myocardial viability
M. Rizwan Khalid, KSA

In current cardiology practice, myocardial viability is a key factor in deciding whether revascularization should be performed especially in patients with previous history of acute myocardial infarction and/or patients with significant ischemic cardiomyopathy. Myocardial viability testing differentiates stunned or hibernating myocardium from infarcted tissue. Revascularization of a coronary artery which supplies an area of viable myocardium may result in improvement in overall cardiac function and better prognosis.

A number of imaging modalities are utilized in evaluating myocardial viability which include cardiac magnetic resonance imaging (CMR), nuclear imaging and echocardiography. CMR with gadolinium has the ability to accurately define infarcted or scarred myocardium. It also can differentiate transmural from sub-endocardial infarcts. Dobutamine CMR assesses contractile reserve and has been validated against dobutamine echocardiography. Nuclear imaging employs either SPECT or PET scanning to evaluate myocardial viability. SPECT imaging can be performed with Thallium (Tl 201) or Technetium (Tc 99). PET scanning utilizes Flouro-deoxy Glucose (FDG); an excellent modality but limited to large centers with PET scans only. Low dose dobutamine Echocardiography is another valuable tool which assesses the contractile reserve of a cardiac region of interest which correlates well with myocardial viability.

This talk will highlight importance concepts in Myocardial Viability and summarize the key imaging modalities being employed to evaluate it in daily practice.
Interplay of cytokines in heart Failure
Pawan K. Singal, Canada

Our understanding of the multiple in vivo functions of the proinflammatory cytokine, tumor necrosis factor (TNFα), is advancing at a rapid pace. In addition to its antitumor effects, overproduction of TNFα provokes tissue injury and organ failure. TNFα has also been shown to be cardiodepressent and responsible for various cardiovascular complications. In spite of this knowledge, the failure of anticytokine immunotherapy indicates that still much needs to be learned for a full comprehension of the role of TNFα in heart biology. Another cytokine, interleukin-10 (IL-10) has been shown to have anti-inflammatory properties. It is suggested to counterbalance many adverse effects of TNFα. IL-10 suppresses the production of TNFα and many other proinflammatory cytokines. TNFα–induced oxidative stress is also known to be mitigated by IL-10. Moreover, improvement in cardiac function after treatment with various drugs is also shown to be associated with an increase in IL-10 content. Based on these data, it is suggested that an optimal balance between IL-10 and TNFα may be a new therapeutic strategy for a healthier heart. (Supported by Canadian Institute for Health Research)

Role of QRS in cardiac resynchronization therapy (CRT)
Nabil El-Sherif, USA

Left ventricular (LV) conduction delay due to left bundle branch block (LBBB) causes regional heterogeneity in contraction and stimulates negative LV remodeling. The conceptual basis of CRT is to minimize LV conduction delay, which improves LV mechanics and induces “reverse” remodeling. Current guidelines support the use of CRT in patients with LV ejection fraction (EF) of 35% or less, NYHA class III or IV, and a prolonged QRS duration (D) of 120 ms or more. However, baseline QRDS which is used as a surrogate for mechanical LV dyssynchrony is not predictive of clinical or echocardiographic response to CRT. Dyssynchrony is not always correlated with QRS duration. While 85% of patients with prolonged QRSD present with dyssynchrony, 30% of patients with dyssynchrony and LVEF of 35% or less have QRSD less than 120 ms. Current criteria for CRT does not include QRS configuration. Recent studies suggest that only patients with LBBB benefit most from CRT, and not patients with RBBB or nonspecific intraventricular conduction defect. 30% of patients with the conventional definition of LBBB may not have true complete LBBB but rather a combination of left ventricular hypertrophy and left anterior hemiblock. Strict criteria for LBBB may have to include QRSD of at least 140 ms in men and 130 ms in women. There are several efforts to improve the predictive value of ECG for response to CRT. In one study, the probability of reverse volumetric LV remodeling during CRT can be accurately predicted by characterization of the ventricular activation sequence before and after CRT with the use of the standard 12-lead ECG. The translational mechanism for volumetric reverse remodeling is activation wavefront fusion, which is evident on the paced ECG. The probability of reverse remodeling is positively influenced by LV conduction delay and negatively influenced by LV scar volume (QRS score) on the baseline ECG. QRSD shortening has also been studied as a predictor of clinical response. There is growing evidence that the ΔQRSD is an independent predictor of the response. A longer (QRSD after CRT is associated with worse mortality or need for transplantation
Echocardiography optimization of CRT
Abdulaziz Al Ghamdi, KSA

Over the past decade, cardiac resynchronization therapy (CRT) has changed the treatment of patients with end-stage, drug-refractor heart failure. Evidence of 8 large trials (including 4,017 patients) and numerous small studies have demonstrated the benefit of CRT on heart failure symptoms, exercise capacity, and systolic left ventricular (LV) function. Various studies demonstrated reverse remodeling after CRT, with a reduction in severity of mitral regurgitation. Moreover, recent data demonstrated a reduction in heart failure hospitalization and mortality after CRT.

However, 20 to 30% of the patients do not benefit from this therapy. Clinical, electrocardiographic and echocardiographic criteria have been studied in an attempt to select patients who will benefit from a cardiac resynchronization therapy, and the echocardiogram is important both in the selection and in the evaluation and optimization of the therapy.

The role of nuclear imaging in CRT
Abdulaziz Al Ghamdi, KSA

Recently, cardiac resynchronization therapy (CRT) has become implemented in the treatment of patients with severe heart failure. Although the improvement in systolic function after CRT implantation can be considerable, 20-30% of patients do not respond to CRT. Evidence is accumulating that the presence of LV dyssynchrony is mandatory for the response to CRT. Since 1980s attempts have been made to assess cardiac resynchronization with nuclear imaging, and it has been reported recently that information on LV dyssynchrony can be obtained from gated myocardial perfusion SPECT with phase analysis. Other studies with SPECT have shown that extensive scar tissue will limit the response to CRT; similarly, it has been demonstrated that viable tissue assessed with SPECT in the target zone for LV pacing lead is needed for a response to CRT. A comprehensive summary will be provided in the presentation on the potential role of nuclear imaging in the selection of patients for CRT.
Electrophysiological substrates of sudden cardiac death
Nabil El-Sherif, USA

Better understanding of the electrophysiological (EP) substrates of sudden cardiac death (SCD) in patients with organic heart disease can impact management strategy. At least 4 major EP substrates are recognized. These are: 1) AP prolongation and dispersion of repolarization; 2) abnormal conduction due to altered connexin, extracellular matrix, and scar tissue; 3) altered neurohumoral signaling; and 4) alterations in intracellular calcium kinetics. The above mechanisms interact with a distinct genetic background. Evidence of the impact of genetic factors include data on family clustering of victims of SCD. Also, evidence that Silent polymorphism or mutations of genes are prevalent in the general public and may contribute to enhanced susceptibility to SCD under specific circumstances such as acute ischemia, hypokalemia, and pro-arrhythmic response to drugs. Several EP alterations associated with post-myocardial infarction (MI) remodeling are arrhythmogenic. These include downregulation of K gene expression, reexpression of fetal isoforms of ICa-L, ICa-T, Na-K ATPase; and Na channel genes. Post-MI alterations of passive membrane properties including downregulation and/or redistribution of connexin 43 and expression of matrix metalloproteinases (MMP) and tissue inhibitors of MMP are also arrhythmogenic. A combination of these alterations can make the post-MI myocardium susceptible to both reentrant rhythms and triggered activity. There is recent data to suggest that qualitative characterization of post-MI scar by cardiovascular magnetic resonance may predict SCD in patients with ischemic cardiomyopathy better than LVEF. On the other hand, the impact of neuroendocrine signaling on susceptibility to SCD is evidenced by the extensive literature showing that increased sympathetic activity and decreased parasympathetic activity are arrhythmogenic. Further, polymorphic variations in ß-1 and ß-2 adrenergic receptors can influence mortality in patients with dilated CMP and that post-MI regional cardiac hyperinnervation (nerve sprouting) may enhance the susceptibility to malignant ventricular tachyarrhythmias. Finally, altered calcium kinetics especially in the setting of acute ischemia/reperfusion can be markedly arrhythmogenic by at least 3 different mechanisms: 1) calcium/voltage alternans; 2) calcium oscillatory Responses, and 3) calcium/voltage uncoupling. Unfortunately, with the exception of alternans in the form of T-wave alternans (TWA), there is currently no other surrogate clinical markers of altered calcium kinetics.

Vulnerable Plaque
M. Rizwan Khalid, KSA

Imaging and detection of the vulnerable plaque is a major break-through in the field of coronary artery disease. It is not only a daunting task but also a therapeutic challenge. It is of prime importance to understand the patho-physiology of the vulnerable plaque and the development of the atherosclerotic plaque. A lot of research has been focused on the thin cap fibro-atheroma and highlight its various features. This includes a thin cap, a large necrotic lipid core and active inflammation. The next step is to study various novel and current diagnostic techniques available to detect vulnerable plaques. A number of therapeutic approaches to treat the vulnerable plaque include both invasive and non-invasive strategies. The SHAPE taskforce has come out with their position paper and underscores the importance of addressing the “vulnerable plaque”, “vulnerable blood”, “vulnerable organ” and the “vulnerable patient”.

This talk will highlight core concepts of the vulnerable plaque and summarize the key imaging modalities being employed to evaluate it in daily practice.
Sleep disordered breathing and cardiovascular risks  
Saleh Al Dammas, KSA

Sleep Disordered Breathing (SDB) is a common problem, SDB includes obstructive Sleep Apnea, Central Sleep Apnea and Upper Airway Resistance Syndrome.

OSA is the commonest form of SDB and has a prevalence of 2 to 4% in the general population. There is a clear causal relationship between OSA and Hypertension with 40% of patients with OSA having hypertension. 50 to 70% of individuals with uncontrolled hypertension have OSA.

OSA is now a well recognized independent risk factor for Coronary Artery Disease (CAD) and Cerebro-Vascular Accidents (CVA) particularly moderate and severe OSA.

Central sleep apnea is seen more with advanced heart failure and could worsen the outcome. There is evidence that sleep apnea patients have a higher incidence of arrhythmias and sudden death. Early diagnosis and intervention (mainly CPAP therapy) could help reducing the cardiovascular risk including CAD and CVA. Patients with suspected SDB must be referred to a sleep specialist for proper diagnosis and therapy.

Reperfusion injury as a target for cardioprotection  
Derek Hausenloy, UK

Despite current therapy, the morbidity and mortality from coronary heart disease (CHD) remain significant in Europe and worldwide. Hence novel therapeutic strategies are required to protect the heart from acute ischaemia-reperfusion injury (IRI) in order to reduce the extent of myocardial infarction, preserve cardiac function and improve clinical outcomes in patients with CHD. The clinical settings of acute IRI in which cardioprotection needs to be further improved include STEMI patients: Myocardial reperfusion using primary percutaneous coronary intervention (PPCI) continues to be improved with recent developments in PCI technology, anti-platelet and anti-thrombotic therapy. However, the full benefits of myocardial reperfusion as mitigated by the presence of lethal myocardial reperfusion injury. There is currently no effective therapy for reducing this form of myocardial injury. Therefore, novel therapeutic strategies need to be identified to reduce lethal myocardial reperfusion injury, in order to further reduce myocardial infarct size, preserve cardiac function and improve clinical outcomes in this patient group.
The heart failure syndrome: implications for exercise training
Michael A. Welsch, USA

Heart failure develops secondary to an insult to the cardiovascular system. The insult results in cardiac, circulatory, and skeletal muscle alterations. These compensatory alterations may initially be effective in normalizing cardiocirculatory function. However, in time, the changes become restrictive, especially during exertion. Consequently, many heart failure patients are frequently hospitalized, suffer from functional limitations, and have a high mortality rate. Management of heart failure patients has become increasingly multidisciplinary, and the composition of the team and relative importance of its members must constantly change depending on the patient’s status. This review outlines factors that contribute to exercise tolerance, a marker of clinical severity of the disease. In addition, the role of exercise training for these patients is defined. Evidence indicates that patients with stable heart failure should participate in exercise training. The guidelines for and components of exercise training are similar to other clinical populations. However, the exercise prescription should be tailored to each patient’s unique demands and goals. As a result of training, many of the peripheral abnormalities improve. These improvements translate to increased exercise tolerance, reduced activity-related symptoms, and improved quality of life. Finally, exercise training increases survival time and decreases health care costs.

Suppression of left ventricular hypertrophy by phosphodiesterase 5 inhibitors: the role of calcineurin and P 38 MAPK
Said Y. Khatib, KSA

Background: Phosphodiesterase-5 (PDE-5) inhibitors, Sildenafil(SILD) and Ordonofil(ORD), have been shown to have cardioprotective effect against ischemic/reperfusion injury and to suppress cardiac hypertrophy. Objectives: To investigate the suppressive effect of PDE-5 inhibitors on Left Ventricular hypertrophy (LVH) in rabbit heart, the attenuation of phenylephrine (PE)-induced hypertrophy in neonatal cardiomyocytes as well as the role of Calcineurin and P38 MAPK. Methods and Results: LVH, induced by 4 weeks of L-NAME treatment (10mg/kg/day) in drinking water was reversed by 16% and 21% with SILD and ORD (50 mg/kg/day) respectively (P<0.05, n=11-14). Neonatal cardiomyocytes, 4 days old, were cultured with or without 10 microM PE in the presence or absence of 0.1 mg/L of both drugs. PE increased the cell surface area of cardiomyocytes by 31% (P<0.05, n=6) and 3H-leucine incorporation by 43% (P<0.05, n=6) after 24 h. The PE-induced hypertrophy was significantly attenuated by 0.1 mg/L of either ORD or SILD. PE induced significant phosphorylation of ERK1/2 (292%, P<0.05, n=6) and p38 (173%, P<0.05 versus control, n=6) at 5 min after treatment, which was significantly inhibited by ORD but not SILD. Moreover, PE-induced hypertrophy was associated with the translocation of p38 MAPK and ERK1/2 to nuclei, which was inhibited by ORD but not SILD. Calcineurin phosphatase activity increased significantly after 1 hr (1.6 fold) or 24 hrs (2 folds) of treatment with PE which was reduced after 24 hr treatment with either drugs (0.1mg/L). Conclusions: PDE-5 inhibitors, effectively suppress cardiac hypertrophy possibly through signaling mechanisms involving inhibition of MAPKs and Calcineurin.
Remote ischemic conditioning as a clinical application
Derek Hausenloy, UK

Coronary Artery Disease (CAD) is the leading cause of death and disability world-wide and early and successful restoration of myocardial reperfusion following an ischemic event is the most effective strategy to reduce final infarct size and improve clinical outcome. This process can however induce further myocardial damage, namely acute myocardial ischemia-reperfusion injury (IRI), and worsen clinical outcome. Therefore novel therapeutic strategies are required to protect the myocardium against IRI in patients with CAD. In this regard, the endogenous cardioprotective phenomenon of “ischemic conditioning”, in which the heart is put into a protected state by subjecting it to one or more brief non-lethal episodes of ischemia and reperfusion, has the potential to attenuate myocardial injury during acute IRI. Intriguingly, the heart can be protected in this manner by applying the ‘ischemic conditioning’ stimulus to an organ or tissue remote from the heart (termed Remote Ischemic Conditioning or RIC). Furthermore, the discovery that RIC can be non-invasively applied using a blood pressure cuff on the upper arm to induce brief episodes of non-lethal ischemia and reperfusion in the forearm has greatly facilitated the translation of RIC into the clinical arena. Several recently published proof-of-concept clinical studies have reported encouraging results with RIC, and large multi-centre randomized clinical trials are now underway to investigate whether this simple non-invasive and virtually cost-free intervention has the potential to improve clinical outcomes in patients with CAD. In my talk, I will provide an update of recently published and ongoing clinical trials in the field of RIC.

Role of mechanical assist devices in myocardial protection
M. Salik Jahania and Robert M. Mentzer Jr. USA

Congestive heart failure (CHF) is the leading cause of morbidity and mortality worldwide. Coronary heart disease leading to acute coronary syndrome (ACS) is one of the leading causes of CHF. Pharmaceutical and percutaneous coronary interventions (PCI) are the mainstays of treatment for ACS. Cardiogenic shock often accompanies ACS, requiring pharmaceutical and mechanical circulatory support until myocardial recovery. Typically mechanical circulatory support consists of intra-aortic balloon counter pulsation (IABP) but this is often incapable of maintaining adequate tissue perfusion. With miniaturized, short term percutaneous, and implantable ventricular assist devices (VADs) the morbidity and mortality associated with cardiogenic shock and CHF has declined significantly. Percutaneous mechanical assist devices can generate 2.5 to 10 liters of flow and may eventually replace the IABP. Use of VADs during and after PCI for ACS may also limit infarct size. And percutaneous right ventricular support will expand the use of VADs in patients with acute and chronic right heart failure.

The of VADs in the setting of post-cardiotomy cardiogenic shock has gained wider acceptance. VADs can now enable enough myocardial recovery to permit their removal or explantation. In the absence of recovery, however, these patients can be bridged to transplantation. And in patients who are not candidates for transplantation, VADs can serve as destination therapy. While the number of heart transplant operations has declined, the use of VADs has increased. Major limitations in the use of VADs include drive site infections, thromboembolic episodes, and hemorrhage and device failure. Should these problems be overcome, one can expect even greater use, perhaps someday even replacing the need for heart transplantation and the problems associated with immunosuppression.
How to achieve myocardial recovery with mechanical assist devices?

Diego Delgado. Canada

Alterations of many molecular pathways are involved in the development of chronic heart failure. Left ventricular assist devices (LVADs) support is accompanied by marked hemodynamic, neurohormonal, physiologic, cellular, and molecular changes indicative of recovery.

LVADs lead to lowered cardiac pressure and volume overload in the myocardium followed by decreased ventricular wall tension, reduced cardiomyocyte hypertrophy, improved coronary perfusion and decreased chronic ischemia. Improved coronary flow and myocardial perfusion as well as decreased ventricular wall tension may possibly alter the molecular systems involved in the development of chronic cardiac insufficiency.

Despite these changes, experience with clinical successes is limited. Recently, several adjunctive therapies were attempted to restore ventricular function.

Structural and functional reverse remodeling associated with LVADs continues to inspire innovative research. The ultimate goal of these investigations is to achieve sustained recovery of the failing human heart. Further studies of topics such as the timing of LVAD implantation and explantation, adjunct medical and surgical therapy, and optimum LVAD weaning protocols might help improve the success of this promising technology.

Revascularization in ischemic cardio-myopathy

Samih Lawand, KSA

The approach towards coronary angioplasty or coronary bypass surgery in patients with left ventricular dysfunction is an issue that has been the center of debate for a long time. The contentious points are those related to myocardial viability and predictors of outcome that should be adopted. The intervention that will not change outcome whether by improving life expectancy and or symptoms should not be considered. Of course the periprocedural risks are not be ignored particularly when taken along with the grim intermediate and long term outcome of many of those patients. The other point of concern is related to completeness of Revascularization and whether a numerically complete Revascularization is equally likely to compare satisfactorily with the less complete as long as the achievable Revascularization plan will result in abolishing sizeable myocardial Ischemia.

The decision towards targeted Revascularization is best carried out by seasoned interventional cardiologists and cardiac surgeons and customized to individual patients needs.
Myocardial regeneration: Finally something that works
Roger Laham, USA

Myocardial infarction (MI), and its resultant left ventricular (LV) dysfunction remain a leading cause of mortality and morbidity. Different therapies for myocardial regeneration have been investigated with varying results. The intrinsic regenerative potential of the myocardium has been increasingly recognized, however, appears to be insufficient to repair myocardial damage resulting from coronary occlusion. Several approaches have been used for myocardial repair including protective cytokines, cell based therapy using bone marrow and stem cells (adult or embryonic), and tissue scaffold with limited success. This has probably been limited by limitations of delivery modalities used with poor survival of transplanted cells (possible related to “milieu”). This, coupled with mounting evidence regarding lack of transdifferentiation potential of adult non-cardiac derived stem cells, warrants a novel approach to myocardial regeneration.

However, Cell based investigational therapies for ischemic heart disease and congestive heart failure have come of age. Although, in its simplest forms, the use of autologous skeletal myoblasts and bone marrow derived cells have reached clinical trials, the promise of such therapy lies in the use of stem cells (resident, circulating or bone marrow derived, pleuripotent or differentiated) for myogenesis. We will describe the status of the field reviewing most available data to date with an emphasis on a novel approach to myocardial regeneration developed in our laboratory with myotissue transplantation. We will describe possible regenerative mechanisms and describe early clinical data and attempt to establish collaborative clinical program in KSA that would result in rapid development of these technologies.

Use of impella in complex coronary interventions
Hassan Mhish, KSA

Not available
Progressive effects of diabetes mellitus on the heart
Frank Christopher Howarth, UAE

The total number of people with diabetes mellitus (DM) is projected to increase from 171 million in 2000 to 366 million in 2030 (1) and type 2 DM accounts for more than 95% of cases. The association between type 2 diabetes and obesity is very strong and cardiovascular disease is the major cause of morbidity and mortality in diabetic patients (2,3). A variety of diastolic and systolic dysfunctions have been demonstrated in type 2 diabetic heart. Hemodynamic abnormalities include reduced left ventricular ejection fraction, impaired diastolic relaxation and filling and reduced peak filling rate with the severity of the abnormalities depending on the patients’ age and duration of diabetes (4). The Zucker diabetic fatty (ZDF) rat is a genetic model in which the male homozygous (FA/FA) animals develop obesity and type 2 diabetes. As in obese humans, ZDF rats exhibit early b-cell compensation (hyperplasia) followed by decompensation (loss of cells). The early changes in b-cell responsiveness to glucose may contribute to the hyperinsulinemia and subsequent insulin resistance (5). The effects of DM on the heart have been investigated in young (9-13 wks) and aged (30-34 wks) ZDF rats and compared to age-matched Zucker lean controls. Blood glucose in young and aged rats was 412±16 and 478±29 mg/dl in ZDF rats compared to 108±3 mg/dl in controls. In young ZDF animals amplitude of shortening was unaltered and time course of myocyte shortening was prolonged. In aged ZDF animals amplitude and time course of myocyte shortening were unaltered. In young and aged ZDF animals amplitude of the Ca²⁺ transient was unaltered, time course of the Ca²⁺ transient was prolonged and amplitude of L-type Ca²⁺ current was reduced. Expression of genes encoding cardiac muscle proteins was variously altered in young and aged animals. For example Cacna1c (Calcium channel, voltage-dependent, L type, alpha 1C subunit) was increased in young and unaltered in aged ZDF ventricle however, Cacna1d (Calcium channel, voltage-dependent, L type, alpha 1D subunit) was unaltered in young and aged ZDF ventricle. Slc9a1 (Solute carrier family 9, Na⁺/H⁺ exchanger) was reduced in young and aged ZDF ventricle. Atp2a1 (ATPase, Ca²⁺ transporting, cardiac muscle, fast twitch 1) was unaltered in young and increased in aged ZDF ventricle whereas Atp2a2 (ATPase, Ca²⁺ transporting, cardiac muscle, slow twitch 2) was reduced in young and aged ZDF ventricle. Myh6 (Myosin heavy polypeptide 6, cardiac muscle, alpha) was decreased in young and aged ZDF ventricle however, Myh7 (Myosin heavy polypeptide 7, cardiac muscle, beta) was increased in young and unaltered in aged ZDF rat (6). Changing expression of genes encoding a variety of cardiac muscle proteins may partly underlie the progressive changes in function and Ca²⁺ signaling in the diabetic heart.
Vascular Health and Performance: linking biochemistry and physiology with physical function
Michael A. Welsch, USA

The endothelium is a key regulator of vascular homeostasis, and acts as an active signal transducer for circulating influences that modify vessel wall function. Changes in endothelial function have profound effects on physical performance and vascular health. In fact, a decline in nitric oxide dependent endothelial function precedes the development of morphological atherosclerotic changes, whereas proper dosing of exercise appears to protect the endothelium from deteriorating. The purpose of the talk is to provide the audience with an update on the current understanding of the role of several biochemical markers believed to influence vascular function and consequently physical performance and health. Specifically, the talk will focus on the manner in which a single bout of exercise alters the balance of nitric oxide, reactive oxygen species and anti-oxidants, and discuss the implications for vascular control and adaptation; examine the vascular changes that occur with aging and their implications for physical function; and discuss the evidence for the role of exercise training in improving vascular function. The information presented aims to provide basic scientists with further insight into the complex nature of vasoregulation and clinicians with practical information regarding the potential of exercise interventions aimed at improving vascular function.

Cell signaling and metabolism in diabetic heart
Frank Christopher Howarth, UAE

The streptozocin (STZ) – induced diabetic rat is a widely used experimental model of type 1 diabetes mellitus (DM). DM is typically induced in young adult rats by a single intraperitoneal injection of STZ (60 mg/kg body weight). The characteristics of STZ-treated rats include hyperglycemia, hypoinsulinemia and dyslipidemia. This abstract summarizes some of the data presented by Choi et al (2002) and a few other researchers on the effects of STZ-induced diabetes on heart function and intracellular Ca^{2+} signaling. In vivo studies have demonstrated reduced heart rate, reduced LV peak ejection rate and peak-filling rate and decreased circumferential shortening velocity in diabetic heart compared to controls (1). Reduced heart rate, lower LV rate of development of systolic pressure and rate of decline of the pressure, longer time to peak (TPK) pressure and time to half (THALF) relaxation from peak pressure was demonstrated in Langendorff-perfused diabetic heart compared to controls (1). Defective electrical conduction as evidenced by reduced sino-atrial conduction time may partly contribute to the reduction in heart rate (2). In myocytes, the rates of contraction and relaxation and amplitude of contraction were lower and TPK and THALF relaxation from peak contraction were longer in diabetic rat compared to controls (1). The rate of rise and rate of decline and amplitude of the Ca^{2+} transient were lower in diabetic myocytes compared to control (1).TPK and THALF relaxation of the Ca^{2+} transient were prolonged in myocytes from diabetic rat compared to controls. Amplitude of intracellular Ca^{2+} concentration [Ca^{2+}]i induced by caffeine was lower in diabetic myocytes compared to controls suggesting that the amount of Ca^{2+} stored in the sarcoplasmic reticulum (SR) was lower in diabetic myocytes. The rate of rise and decline of caffeine-induced Ca^{2+} transients were prolonged in diabetic myocytes. Experiments which varied external concentration of Na^+ and Ca^{2+} suggested that the reduction in the rate of decline in the caffeine-induced Ca^{2+} transient might partly be attributed to defective efflux of Ca^{2+} on the Na^+/Ca^{2+} exchange (1). L-type Ca^{2+} current and the voltage-dependence of myocyte shortening were also reduced in diabetic myocytes compared to controls (1,3). Levels of SERCA protein was decreased in diabetic heart compared to controls (1). Collectively, these data suggest that defects in intracellular Ca^{2+} signaling caused by alteration of expression and function of the proteins that regulate [Ca^{2+}]i contribute to functional defects in STZ-induced diabetic rat heart.
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